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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,382	02/11/2008	Shi Du Yan	68548-PCT-US/JPW/JW	4714

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
04/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,382	YAN ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,25 and 26* is/are pending in the application.

4a) Of the above claim(s) *4,6-8,18,20-22,25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,9-17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Gregory S. Emch, Art Unit 1649.

Election/Restrictions

Applicant's election of Group I, claims 1-5 and 9-19, drawn to a method for treating a subject to reduce neuronal damage via administering a RAGE antibody to a subject, and of the species of cell death in the hippocampus, in the reply filed on 06 January 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). However, the election of species requirement set forth in the office action dated 03 December 2008 is hereby withdrawn on the grounds that examining all of the species together does not represent a tremendous search burden.

Claims 1-22, 25 and 26 are pending in the instant application. Claims 6-8, 20-22, 25 and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06 January 2009.

Claims 1-5 and 9-19 are under examination in the instant office action.

Information Disclosure Statement

A signed and initialed copy of the IDS paper filed 27 April 2006 is enclosed in this action.

Further, the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 9-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-4 and 9-18 require the use of an inhibitor of receptor for advanced glycation endproducts (RAGE). Inhibitors of RAGE are described at p.10, lines 19-29 of the specification and can include an antibody which, when contacted with RAGE, specifically inhibits binding between RAGE and a ligand thereof, an anti-sense molecule

which specifically inhibits the expression of RAGE in a cell, an RNAi molecule which specifically inhibits the expression of RAGE in a cell, or a catalytic nucleic acid which specifically inhibits the expression of RAGE in a cell. However, the list is exemplary and not limiting. Furthermore, the specification does not describe which amino acid residues or nucleic acid residues are present in the genus of claimed RAGE inhibitors. The specification fails to disclose which regions of RAGE inhibitors are responsible for reducing neuronal damage, which is stated to be common to all members of the genus. In the absence of a known or disclosed correlation between structure and function, claims which encompass variants defined by their function are generally not considered described.

Applicants are directed to the recently-published guidelines on interpretation of the written description requirement, available on the internet at: http://www.uspto.gov/web/menu/written.pdf . See in particular Examples 9, 10 and 12 drawn to protein variants and antisense oligonucleotides, including those claimed by their functions. Since the specification does not disclose which amino acid and/or nucleic acid residues are common to all RAGE inhibitors and or which structures are either necessary or sufficient such that members of the genus have the required activity, the claims do not meet the written description requirement. See also MPEP §2163 (II)(3), which states, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d

1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 9-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ganesh et al. (Targeted disruption of the Epm2a gene causes formation of Lafora inclusion bodies, neurodegeneration, ataxia, myoclonus epilepsy and impaired behavioral response in mice. Hum Mol Genet. 2002 May 15;11(11):1251-62), in view of Yan et al. (Nature, 1996, citation 5 on IDS dated 27 April 2006), further in view of Lado et al. (Seizure-induced hippocampal damage in the mature and immature brain. Epileptic Disord. 2002 Jun;4(2):83-97).

The claims are directed to a method for treating a subject either during or soon after a seizure, in order to reduce the extent of neuronal damage in the subject resulting from the seizure comprising administering to the subject, either during or soon after the seizure, a therapeutically effective amount of an inhibitor of receptor for advanced glycation endproducts (RAGE), so as to thereby reduce the extent of neuronal damage in the subject.

The Ganesh reference teaches that advanced glycation endproducts (AGEs) are specifically associated with neurons in a mouse model of epilepsy, i.e. a mouse model of Lafora disease, which is characterized by seizures, cellular dysfunction, cell death and eventual death (p.1251-1252, Abstract and Introduction). Ganesh teaches that the human disease and animal model are characterized by cytoplasmic inclusions (Lafora bodies) present in neurons, including those of the hippocampus and cerebral cortex, which also co-expressed the AGEs (p.1252, Results, paragraph 2). Ganesh teaches that the mouse model was characterized by extensive neuronal cell death in the hippocampus (p.1252, Results, paragraph 4) and explicitly states that the Lafora inclusions may induce neurotoxicity through and interaction between AGEs and the receptor for advanced glycation endproducts (paragraph spanning pp.1259-1260).

Although the Ganesh reference strongly suggests that blocking the interaction between AGE and RAGE would be desirable for treating the neuronal damage in the cerebral cortex and hippocampus associated with this seizure disorder, the reference does not explicitly teach administration of an inhibitor of RAGE either during or soon after a seizure to reduce the extent of neuronal damage, as claimed. However, upon reading the Ganesh disclosure, the skilled artisan would have recognized the desirability of developing methods of treating neuronal damage (including that of the hippocampus), which results from the association of AGEs and RAGE. Furthermore, the Yan reference teaches that RAGE mediates the effects of the Aβ peptide on neurons and microglia and that there is increased expression of RAGE in damaged brain tissue in Alzheimer's disease, indicating that RAGE is relevant to the cell death in

such damaged brain tissue (abstract). The Yan reference teaches that experiments with RAGE and RAGE blocking antibody confirmed that RAGE specifically bound Aβ and mediated oxidant stress and neuronal damage, (which can be blocked by the antibody) (p.691, paragraph 2).

Although the Yan reference teaches that blocking the interaction between another ligand for RAGE (Aβ) and RAGE with an antibody that specifically inhibits binding between RAGE and the ligand thereof would be desirable for treating the neuronal damage in Alzheimer's brain tissue, the reference does not explicitly teach administration of an inhibitor of RAGE either during or soon after a seizure to reduce the extent of neuronal damage, as claimed. However, the Lado reference teaches that neuronal damage in the hippocampus may occur immediately after the first seizure in a human patient and that early aggressive treatment of seizures is preferred (p.5, final paragraph).

Therefore, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention to arrive at the claimed invention by combining the disclosures of Ganesh et al., Yan et al. and Lado et al. Given Lado's teaching that treatment should occur immediately, it would have been obvious to the artisan to treat with the antibody either during or soon after the seizure, as in claims 1, 9 and 15. Further, Ganesh, Yan and Lado all teach data from diseases that occur in humans, as in claims 2 and 16. All of the references teach disorders that involve neuronal damage resulting from cellular dysfunction and cell death in the hippocampus and cerebral cortex, as in claims 3, 4, 17 and 18. As set forth above, Yan teaches an antibody that

when contacted with RAGE specifically inhibits binding between RAGE and a ligand thereof, as in claims 5 and 19. None of the references explicitly teach administration within three days of the seizure, within one day, within six hours, within one hour or within 20 minutes of the seizure, as in claims 10-14, respectively. However, in the instant case the administration regime is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize (see MPEP §2144.05). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal administration regime given Lado's teaching that treatment should occur early after a seizure. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of administration regime would have been obvious at the time of applicants' invention.

As evidenced by Ganesh, the skilled artisan would have known that AGEs are associated with neuronal damage in the hippocampus and that inhibiting binding of AGE and RAGE to reduce the neuronal damage would be desirable for treating subjects with seizure disorders. As evidenced by Yan, the skilled artisan would have known that ligand-RAGE binding is implicated in the neuronal damage associated with Alzheimer's disease and that treatment of a subject with an antibody which inhibits ligand-RAGE binding would be effective in reducing neuronal damage. As evidenced by Lado, the skilled artisan would have known that hippocampal neuronal damage can occur immediately after the first seizure in a human and that early aggressive therapy for seizures in desirable. Given Ganesh's teaching that AGE/RAGE is implicated in

neuronal damage/cell death in the hippocampus and given Yan's teaching that a RAGE blocking antibody would reduce neuronal damage in Alzheimer's disease, it would have been reasonable to predict that such antibody to RAGE could be successfully used to reduce the neuronal damage resulting from seizures, as claimed. Yan's results with Alzheimer's disease related pathology supports a reasonable expectation of success. Further, the motivation to combine the references flows logically from the disclosures of said references.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
24 April 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
April 24, 2009